UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/790,544	03/01/2004	Miroslav Colic	4904-4DIV	9685

7590 02/03/2009

COHEN, PONTANI, LIEBERMAN & PAVANE
Suite 1210
551 Fifth Avenue
New York, NY 10176

EXAMINER	
XIE, XIAOZHEN	
ART UNIT	PAPER NUMBER
1646	

MAIL DATE	DELIVERY MODE
02/03/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/790,544	COLIC, MIROSLAV	
	Examiner	Art Unit	
	XIAOZHEN XIE	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 November 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *15,17-22 and 24* is/are pending in the application.

4a) Of the above claim(s) *20* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *15, 17-19, 21, 22 and 24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Response to Amendment

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office Action has been withdrawn pursuant to 37 CFR 1.114.

Applicant's amendment of the claims filed 10 November 2008 has been entered. Applicant's remarks filed 10 November 2008 are acknowledged.

Claims 1-14, 16 and 23 are cancelled. Claim 24 has been added. Claims 15, 17-22 and 24 are pending. Claim 20 is withdrawn from further consideration as being drawn to a nonelected species. Claims 15, 17-19, 21, 22 and 24 are under examination to the extent they read on the elected species (i.e., the pharmaceutical composition further comprises pro-oxidant metal complexes and a cytokine which is IL-12).

Claim Rejections Maintained

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 15, 17-19, 21, 22 and 24 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for:

(1) a method of treating a tumor in a patient comprising orally administering to the patient a pharmaceutical composition comprising a zeolite having an average particle size of about 6 microns or less, wherein the composition further comprises a pro-oxidant metal complex; and

(2) a method for treating a tumor in a patient comprising intravenously administering to the patient a pharmaceutical composition comprising a clinoptilolite having a mean particle size of 250 nm;

does not reasonably provide enablement for an oral zeolite pharmaceutical composition further comprising a cytokine, such as IL-12; nor provide enablement for intravenously administering a pharmaceutical composition comprising any zeolite having a mean particle size of 250 nm. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. The basis of this rejection has been set forth in the previous office actions, also as the following.

Applicant argues that independent claim 15 has been amended to recite "a method of treating a tumor in a patient comprising orally administering to the patient a pharmaceutical composition comprising a zeolite having an average particle size of about 6 microns or less". Applicant argues that limiting the claimed method to be an oral-administration-based therapy obviates the nonenablement of intravenous zeolite administration. Applicant also argues that new claim 24 provides a method for treating a tumor comprising intravenously administering a zeolite composition, and the zeolite used in this method has a mean particle size of 250 nm, which the Examiner has

already stated explicitly that such method is enabled, regardless of the form of administration (i.e. intravenous or otherwise).

Applicant's argument has been fully considered but has not been found to be persuasive.

The amended claims are now directed to the use of two types of zeolite-containing pharmaceutical compositions for treating a tumor: 1) an oral pharmaceutical composition comprising a zeolite having an average particle size of about 6 microns or less, wherein the oral composition further comprises at least one of a pro-oxidant complex and a cytokine, e.g., IL-12; and 2) an intravenous pharmaceutical composition comprising a zeolite having a mean particle size of 250 nm.

As set forth previously, Applicant has disclosed in the instant specification three different uses of the nano-engineered zeolite in a pharmaceutical setting for treating a tumor: 1) the nano-engineered zeolite can be used to encapsulate metal complexes that act as an anti-oxidants or pro-oxidants (catalytic salen-metal anti-oxidants or pro-oxidants with cobalt, manganese, ion, rhodium and palladium) (Example I). In this case, a mean particle size is about 500 nm (pp. 16, lines 10-17). The disclosure shows in Example IV that the nano-engineered zeolite was administered in the form of a mice chow (orally) to mice of various tumor models (lung, colorectal, and breast adenocarcinoma and melanoma), and exhibited anti-cancer activity in the animals (pp. 32, lines 5-19). 2) Clinoptilolite with a mean particle size of 250 nm can be used as a vaccine adjuvant to enhance the immunogeneity of proteins, cell parts or whole cell vaccines. In such case, the clinoptilolite was injected near the tumor site to attract

lymphocytes, and significant infiltration of lymphocytes and tumor remission were observed with melanoma, adenocarcinomas of lung and colorectal models (Example VII); and 3) the zeolite can be used to incorporate small drugs, macromolecules or whole cells for a delayed sustained release.

With respect to the oral administration-based therapy, Applicant has not provided sufficient guidance and support for an orally administered zeolite-containing pharmaceutical composition comprising a cytokine, such as IL-12. While the instant inventor has found that orally administered, finely ground clinoptilolite is nontoxic and useful in cancer treatment, and the prior art (Nojiri et al., EP 681841 A1) teaches that a zeolite encapsulating a free-radical generator can exhibit anti-cancer activity upon orally administered to a human body, however, neither the specification, nor the prior art, provides teachings that IL-12 can be delivered orally in the form of a zeolite composition, and maintains its immunological or anti-tumor activity. Colombo et al. (Cytokine Growth Factor Rev., 2002, Vol. 13(2):155-168) reviewed studies and clinical trials using IL-12 in anti-tumor immunity and immunotherapy, and all of which used injection for administering IL-12 for treating cancer.

With respect to the method based on intravenous administration of a pharmaceutical composition comprising a zeolite having a mean particle size of 250nm, the previous office action (mailed on 9 May 2008) indicates that the **clinoptilolite** having a mean particle size of 250 nm is enabled. There is no record indicating enablement for any zeolite having a mean particle size of 250 nm for intravenous administration. What Applicant has disclosed in Example VII is the use of ground,

natural highly crystalline clinoptilolite as an adjuvant component for enhancing immunogeneity. Applicant discloses that those ground particles have rough edges and can penetrate successfully inside cells. Applicant, however, does not teach that any type of zeolite can be used similarly. As stated previously, not all types of zeolite can be used in a therapeutic setting, for example, Brown et al. (EP0384070, reference provided previously) teach that zeolite P with particle sizes in the range from 0.1 to 5.0 microns (falling within the scope of the recited range) is used in detergent compositions.

Therefore, without detailed guidance or working example from the specification, the artisan would need to generate a large number of zeolite-containing compositions encompassed by the claims, and determine their efficacy in cancer treatment. The scope of patent protection sought by Applicant as defined by the claims fails to correlate reasonably with the scope of enabling disclosure set forth in the specification. The artisan would not know how to practice the invention as broadly claimed without undue experimentation.

New Grounds of Rejection

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 15 and 19 are rejected under 35 U.S.C. 102(b) as being anticipated by Nojiri et al. (EP 681841 A1, Date of Publication: 15 November 1995).

The claims are directed to a method of treating a tumor in a patient comprising orally administering to the patient a pharmaceutical composition comprising a zeolite having an average particle size of about 6 microns or less (claim 15); wherein the pharmaceutical composition further comprises at least one of a pro-oxidant metal complex, zinc, silver, a cytokine, a cell, and a tumor antigen (claim 19).

Nojiri et al. teach an *in vivo* free-radical generator comprising silver ions (a pro-oxidant metal complex) supported on a specified carrier, such as zeolite or silica, for administration to a human body. Nojiri et al. teach that the released free radicals (.OH) act on cancer cells to thereby suppress the cell growth and disrupt the cells, thus making cancer therapy possible (see Abstract). Nojiri et al. teach that the carrier is finely pulverized to have a particle diameter of about 1 micron, and mixed in a solvent to form slurry, so that it can be administered into a human body by orally (pp. 5, lines 34-37). Nojiri et al. showed the medicinal efficacy of the free-radical generator on three different types of cancer cells, human acute promyelocytic leukemia cell HL-60, human esophageal squamous cancer cell ES-2, and human malignant glioma cell A172 (pp. 7, Example 2). Therefore, Nojiri et al. anticipate the instant claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claim 17 is rejected under 35 U.S.C. 103(a) as being unpatentable over Nojiri et al. (EP 681841 A1), in view of Rodriiguez-Fuentes et al. (Zeolite, 1997, Vol. 19:441-448).

Nojiri et al. teach as set forth above. Nojiri et al., however, do not teach that the zeolite is clinoptilolite (claim 17).

Rodriiguez-Fuentes et al. teach the use of a particular type of zeolite, the purified natural clinoptilolite NZ, in a therapeutic setting. Rodriiguez-Fuentes et al. teach that a durg based on the purified natural clinoptilolite NZ is safe and nontoxic for human use.

It would have been *prima facie* obvious to one of the ordinary skill in the art at the time the invention was made to use purified natural clinoptilolite NZ for preparing the pharmaceutical composition of Nojiri et al. One of ordinary skill in the art would have been motivated to do so because Nojiri et al. teach a zeolite-containing composition for treating tumors, and Rodriiguez-Fuentes et al. teach a specific form of zeolite, i.e., the purified natural clinoptilolite NZ, that is safe and non-toxic for human use. Therefore, the combined teachings provide a reasonable expectation of successfully making a cancer therapeutic composition.

Claim 22 is rejected under 35 U.S.C. 103(a) as being unpatentable over Nojiri et al. (EP 681841 A1), in view of Carroll (US 6,375,634 B1, which has a priority filing on 19 November 1997).

Nojiri et al. teach as set forth above. Nojiri et al., however, do not teach treating a lung cancer and a colorectal cancer (claim 22).

Carroll teaches that catalyzing free-radical reactions by metals can increase cancer cell destruction (col. 22, line 60 bridging col. 23, line 10), and is useful for treating cancer, e. g., lung and colorectal cancer (col. 21, lines 57-65).

It would have been *prima facie* obvious to one of the ordinary skill in the art at the time the invention was made to apply the free-radical generator composition taught by Nojiri et al. for treating a lung or colorectal cancer. One of ordinary skill in the art would have been motivated to do so because Nojiri et al. teach that the released free radicals (.OH) from the composition act on cancer cells to thereby suppress the cell growth and disrupt the cells, and Carroll further teaches that free-radicals catalyzed by metals can be used for treating lung and colorectal cancer. Therefore, the combined teachings provide a reasonable expectation of successfully treating a lung and colorectal cancer.

Conclusion

NO CLAIM IS ALLOWED.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Xiaozhen Xie whose telephone number is 571-272-5569. The examiner can normally be reached on M-F, 8:30-5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary B. Nickol, Ph.D. can be reached 571-272-0835. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Xiaozhen Xie, Ph.D.
January 28, 2009

/Gary B. Nickol /
Supervisory Patent Examiner, Art Unit 1646